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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,731	11/16/2006	Susanne Alenfalk	133087.10701(101340-1PUS)	9947

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,731	ALENFALK ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *18 and 19* is/are allowed.

6)☒ Claim(s) *1-17, 20-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :11/16/2006;01/30/2008;10/01/2008(2);01/13/2009 .

DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., ***In re Berg***, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); ***In re Goodman***, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); ***In re Longi***, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); ***In re Van Ornum***, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); ***In re Vogel***, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and ***In re Thorington***, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 12-17, 20-28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-37 of U.S. Patent No. 7470678. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is extensive overlap, as these claims fall within the ambit of the patent. The patent has the species excluded by the second proviso species (see last species of claim 17 of the patent). Although the proviso means that claim 1 does not literally embrace that species, it does embrace obvious variants thereof, e.g. the 3-F-phenyl position isomer of the 4-F-phenyl species. Similarly, the first proviso species falls within the patent claim, and appears in the patent as example 25.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "cholesterol-associated tumor" is indefinite. This is not a well defined category of tumors. It isn't even clear whether this would refer to tumors which a) are suppressed by cholesterol or b) tumors which are caused by cholesterol, or caused by elevated levels of cholesterol or c) tumors of cells in the body which produce cholesterol or d) the term covers two, or all of these. Further, it's unclear whether "cholesterol" refers to HDL cholesterol, LDL cholesterol, some other type, or perhaps any type.

Claims 1-10, 12-17, 20-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other forms, does not reasonably provide enablement for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims, insofar as they embrace solvates are not enabled. The numerous examples presented all failed to produce a solvate. The evidence of the specification is thus

clear: These compounds do not possess the property of forming solvates; there is no evidence that such compounds even exist. Thus, this is a circumstance where the "specification is evidence of its own inadequacy" (***In re Rainer***, 377 F.2d 1006, 1012, 153 USPQ 802, 807). These cannot be simply willed into existence. As was stated in ***Morton International Inc. v. Cardinal Chemical Co.***, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here: there is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

Claims 21-25 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims lacks description in the specification. The compound of formula XV is not taught as a pharmaceutical. It is an intermediate, designed to be reacted with (VII).

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The proviso makes no sense. The two excluded species aren't within XV in the first place, because XV is an intermediate, and the species are final products.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Step (ii) at the end of the claim makes no sense. There is no mention of protecting groups anywhere in the claim.

Claims 20 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Step (i) cannot be enabled for such scope. It would cover for example, converting compound with R4=ethyl into a compound with R4=methyl. How would that be done?

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "N^6" is not correct in the first name. Assuming that applicants mean the acetyl attached to the ε-amino group on the lysine itself (the side chain), it is at the epsilon position and should be N(epsilon) or N^{ε} or N_{ε}.

Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The second species has a brace before the azetidinone, but a bracket is needed.

Claims 15-16 and 23-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The prevention and treatment of Alzheimer's Disease and the prevention and treatment of cholesterol-associated tumors with such compounds is not deemed enabled

Pursuant to ***In re Wands***, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see ***In re Vaeck***, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims. A) scope of compounds. Owing to the fact that there are six variables, most with a very broad scope, trillions of compounds are covered. B) Scope of disorders. Alzheimer's Disease is a single disease. The scope of "cholesterol-associated tumors", for reasons set forth above, is unknown.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See ***In re Fisher***, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information on page 16 gives at its smallest a hundred-fold daily dosage range. Moreover, this is generic, the same for the many disorders covered by the specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for Alzheimer's Disease or "cholesterol-associated tumors".

(4) State of the Prior Art: These compounds are unfused azetidinones with a particular substitution pattern at all 4 positions. So far as the examiner is aware, no unfused azetidinones of any kind have been used for the treatment of Alzheimer's Disease or any cancer at all.

(5) Working Examples: There are none. In fact, there is no biological data of any kind.

(6) Skill of those in the art: The skill level for Alzheimer's Disease is considered low. Alzheimer's Disease is an extraordinarily difficult disease to treat, and has been the subject of a vast amount of research, exceeded in recent years only by research into AIDS and

cancer. The channel hypothesis of Alzheimer's disease proposes that the beta-amyloid peptides which accumulate in plaques in the brain actually damage and/or kill neurons by forming ion channels. An abnormal phosphorylation of tau proteins is being investigated as one of the important events in the process leading to their aggregation. There appears to be a specific alteration of a p53-mediated intracellular pathway involved in sensing and repairing DNA damage in peripheral cells, and the role of neuronal apoptosis is under investigation. But even as of 2007, there are great unknowns relating to the links between amyloid-ß and tau, to the mechanisms that determine the selective vulnerability of defined neuronal and glial populations, and to the molecular species that cause nerve cell degeneration. Many kinds of therapies have been investigated in the past, including Hydergine-LC (actually approved by the FDA for Alzheimer's Disease, but later determined to make the disease worse), Cu/Zn chelators (or Cu and Zn homeostasis regulators), endothelin B receptor agonists, α-TNF inhibitors, angiotensin II receptor antagonists, ACE inhibitors, EAA agonists (including partial agoinists), estrogens, metabotropic receptor agonists, muscarinic M2 receptor antagonists, free-radical scavengers, butyrylcholinesterase inhibitors, cholinergic agonists, potassium-channel blockers, P38 kinase inhibitors, sigma-1 Receptor Agonists, 5-HT1A receptor antagonists, α secretase stimulants, and others. From this immense body of work, only two kinds of drugs ever emerged. Four Acetylcholinesterase inhibitors were found to have some limited value: tacrine (Cognex®, no longer clinically used); donepezil (Aricept®); galantamine (Razadyne®/Reminyl®/Nivalin®) and rivastigmine (Exelon®). In addition, one voltage-dependent NMDA-antagonist, Memantine (Axura®/Akatinol®/Namenda®/Ebixa®) was also found effective. Categories of agents and techniques under investigation as of 2007 include

Aß aggregation inhibitors, assorted antioxidants, γ-Secretase modulators, γ-Secretase inhibitors, NGF mimics, PPAR agonists, HMG-CoA reductase inhibitors (statins), Ampakines, Calcium channel blockers, GABA receptor antagonists, Glycogen synthase kinase inhibitors, Intravenous immunoglobulin, Muscarinic receptor agonists, cholinesterase inhibitors, Nicotinic receptor modulators, Passive Aß immunization, Phosphodiesterase inhibitors, Serotonin receptor antagonists, Active Aß immunization, NGF gene therapy, H_3-receptor antagonists, NSAIDs (including NO-NSAIDs and COX-2 Inhibitors), and CB_1 and CB_2 cannabinoid receptor agonists. It is or course entirely possible that one or more of these will eventually be made to work. However, as can be seen by the many, many categories of drugs which never panned out, so simply being the subject of active investigation is no indication that enablement is present at that time. The skill level in this art is so low that only Acetylcholinesterase inhibitors and NMDA-antagonists have been made to work.

An additional complication is that there is no good physiological test for Alzheimer's Disease; one must rely on assorted psychological tests. A definitive diagnosis of Alzheimer's Disease can only be done post mortem.

Preventing Alzheimer's Disease is also completely beyond the skill of medical science. None of the few drugs which have effect of Alzheimer's Disease can prevent the disorder.

As for "cholesterol-associated tumors", no cholesterol regulating agents have ever been established as effective against the treatment of cancer.

(7) The quantity of experimentation needed: Owing to the factors listed above, especially in points 1, 4, 5 and 6, experimentation needed will be extensive.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. ***In re Wright***, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Specification

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark L. Berch/
Primary Examiner, Art Unit 1624

9/17/2009